Effectiveness and Safety of Long-Term Antidepressant Treatment in Bipolar Disorder

S. Nassir Ghaemi, M.D.; Mara S. Lenox, B.A.; and Ross J. Baldessarini, M.D.

Objective: We sought to review research on use of antidepressants for long-term treatment of bipolar depression.

Method: We conducted a computerized literature search of the MEDLINE, *HealthStar*, *Current Contents*, *PsychInfo*, and National Library of Medicine databases to identify studies involving antidepressant, anticonvulsant, or lithium use in bipolar disorder or manic-depressive illness published from 1966 through 2000.

Results: Only 7 blinded, controlled trials of long-term antidepressant treatment in bipolar disorders were found. The available information is not adequate to support the safety or effectiveness of long-term antidepressant treatment for bipolar depression, with or without mood-stabilizing cotherapy.

Conclusion: Antidepressant treatment of bipolar depression is extraordinarily understudied. Controlled trials comparing specific antidepressants, particularly to compare mood-stabilizing agents given alone and combined with an antidepressant, are needed.

(J Clin Psychiatry 2001;62:565–569)

Received Feb. 21, 2001; accepted May 7, 2001. *From the Consolidated Department of Psychiatry and the International Consortium on Bipolar Disorders Research, Harvard Medical School, Boston (Drs. Ghaemi and Baldessarini); the Bipolar Disorder Research Program and the Psychopharmacology Program, Cambridge Hospital, Cambridge (Dr. Ghaemi and Ms. Lenox); and the Bipolar & Psychotic Disorders and Psychopharmacology Programs and Laboratories for Psychiatric Research, McLean Division of Massachusetts General Hospital, Belmont, Mass. (Dr. Baldessrini).*

Supported in part by National Institutes of Health (NIH) grant MH-47370, an award from the Bruce J. Anderson Foundation, and by the McLean Private Donors Neuropsychopharmacology Research Fund (Dr. Baldessarini); and by NIH research career development award grant MH-64189 (Dr. Ghaemi).

Reprint requests to: S. Nassir Ghaemi, M.D., Cambridge Hospital, Department of Psychiatry, 1493 Cambridge St., Cambridge, MA 02139 (e-mail: nassir_ghaemi@hms.harvard.edu).

Bipolar depressive episodes tend to last longer than manic episodes,[1] account for the majority of time ill,[1,2] are particularly distressing to patients,[3] and can be more challenging and dangerous to treat than mania.[4,5] Yet, despite the obvious clinical and public health importance of bipolar depression, it has received remarkably little research attention compared with nonbipolar depression or mania in bipolar disorder.[6–8] Indeed, known bipolarity is typically an exclusion criterion in trials of innovative treatments for depression.[6]

Despite an apparent dearth of evidence concerning the effectiveness and safety of antidepressant treatment in bipolar depressed patients, antidepressants evidently are commonly used for this purpose—possibly even more frequently than mood-stabilizing agents, including lithium and anticonvulsants.[1,8,9] An analysis of 1998 marketing data[10] indicated that valproate and fluoxetine were tied for the largest number of prescriptions for patients diagnosed with bipolar disorder. Sertraline and paroxetine followed, and lithium was only the fourth most prevalent agent. Combinations of a mood stabilizer with an antidepressant were not documented, but may also be a common practice. These observations serve to highlight the compelling nature of bipolar depression to both patients and physicians, the difficulty of differentiating bipolar and unipolar depressive syndromes, and the possibly limited recognition of the risks likely to arise in treating bipolar disorder patients with antidepressants without a mood stabilizer.[6]

To evaluate what is known from research on antidepressant use in bipolar disorder, we conducted a computerized literature search for studies carried out for at least 6 months, to include periods of risk for potential destabilizing effects of antidepressants in this disorder.[3,6] We found only 7 double-blind, controlled, long-term studies that include data pertaining to antidepressant outcomes in bipolar depression, and even these have methodological limitations.

METHOD

We carried out a computerized literature search for reports of studies using the terms *antidepressant*, *anticonvulsant*, and *lithium* in *bipolar disorder* or *manic-depressive illness*, using the MEDLINE, *HealthStar*, *Current Contents*, and *PsychInfo* databases provided by Ovid Technolo-

Table 1. Blinded, Controlled Trials of Long-Term Antidepressant Treatment in Bipolar Disorders[a]

Study	Diagnoses (N)	Treatments	Duration (mo)	Outcome	Results[b]
Prien et al, 1973[11]	BP I (44)	Li vs IMI vs PBO	Up to 24	Hospitalized or new treatment	Efficacy: Li > IMI = PBO
Wehr and Goodwin, 1979[12]	BP I (5)	Li vs Li + DMI	27 (mean)	Nurse ratings	Efficacy: Li + DMI > Li Switch and cycling rate: Li + DMI >> Li
Quitkin et al, 1981[13]	BP I (75)	Li vs Li + IMI	19 (mean)	RDC episodes	Efficacy: Li = Li + IMI Mania: Li + IMI > Li (women)
Kane et al, 1982[14]	BP II (22), UP (27)	Li vs IMI vs Li + IMI vs PBO	11 (mean)	RDC episodes	Efficacy: Li > PBO, IMI = PBO
Prien et al, 1984[15]	BP I (117)	Li vs Li + IMI vs IMI	Up to 24	RDC episodes	Efficacy: Li = Li + IMI Mania: IMI > Li + IMI = Li
Sachs et al, 1994[16]	BP I (15) (19 treatment trials)	Li + BUP vs Li + DMI	Up to 12	DSM-III-R episodes	Efficacy: Li + BUP = Li + DMI Mania: DMI > BUP
Amsterdam et al, 1998[17]	BP II (80), matched UP controls (89), unmatched UP controls (661)	FLX vs PBO	Up to 14	DSM-III-R episodes	Efficacy: FLX similar in BP II and UP Switch rate: BP II > UP

[a]Abbreviations: BP = bipolar disorder (type I or II), BUP = bupropion, DMI = desipramine HCl, FLX = fluoxetine; IMI = imipramine HCl, Li = lithium carbonate, PBO = placebo, RDC = Research Diagnostic Criteria, UP = unipolar major depressive disorder. Symbols: > = more effective than, >> = much more effective than. Efficacy results are for bipolar depressive symptoms or episodes unless stated otherwise.

gies, Inc., as well as the National Library of Medicine database, to cover the era 1966 through 2000. We extended the search through the bibliographies of identified reports and of recent reviews on the treatment of bipolar disorder patients.[3,6,8] Studies were accepted for analysis if they included patients diagnosed with bipolar I or II disorders based on RDC or DSM-III or IV criteria who were treated under double-blind conditions for at least 6 months and if they compared at least one antidepressant with an active comparison treatment or placebo. To expand the potential data collected, no limits were imposed for outcome measures or numbers of subjects. The limited findings obtained, and their questionable comparability across studies, precluded use of quantitative meta-analysis to pool results. Averages are reported as means ± SD unless stated otherwise.

RESULTS

Our search identified only 7 studies meeting entry criteria. Salient characteristics of these trials are summarized in Table 1. Since there were so few studies reported, their essential findings are summarized as follows.

Prien et al. (1973)

In this early study,[11] 44 patients with bipolar disorder were randomly assigned to treatment with lithium, imipramine (mean daily dose = 125 mg), or placebo for 2 years following hospitalization for acute major depression. Outcome was defined as a recurrence of depression or mania requiring rehospitalization or a change of treatment in response to emerging acute symptoms. In the 44 bipolar I subjects, lithium was more effective than imipramine or placebo in preventing recurrences of depression as well as mania, but imipramine was not more effective than placebo against bipolar depression. Recurrence rates for mania or depression, at months 5 through 24, were 18% for lithium-treated subjects vs. 67% in both the imipramine and placebo groups (Fisher exact p = .02), suggesting that the antidepressant was neither helpful nor obviously deleterious.

Wehr and Goodwin (1979)

In another small early study,[12] 5 initially depressed women with RDC bipolar I disorder with previous episodes of mania were observed intensively on an inpatient research unit for 2 years, during which they were given lithium carbonate with desipramine, or lithium alone, at different times. Although the proportion of time in depression diminished with the antidepressant added, cycles of recurrences of mania and depression were nearly 4-times shorter (33 ± 14 days) than with lithium alone (127 ± 50 days), with a corresponding increase in manic recurrences. Despite the small number of patients and complex results, the findings indicate that adding desipramine failed to improve affective stability and may have worsened it.

Quitkin et al. (1981)

This study[13] randomly assigned 75 patients with RDC bipolar I disorder who had a history of mania to maintenance treatment with lithium carbonate alone, or with imipramine added, for a mean of 18.8 months, following at least 6 months of stable mood during treatment with lithium alone. Risk of at least 1 recurrence of a manic episode in subjects treated with imipramine plus lithium was about twice that with lithium alone (significant only in women), with no difference in a low risk of new depressive episodes (approximately 10% overall). The low rate of depressive recurrences with lithium in all subjects,

already selected for lithium responsiveness, severely limited power to test for a potential beneficial effect of the antidepressant, but the results indicate no gain in protection against bipolar depression, and instead, greater mood instability when imipramine was added to lithium.

Kane et al. (1982)

The only prospective, controlled study of maintenance treatment in RDC bipolar II disorder[14] involved 22 bipolar II and 27 unipolar depressive patients stable for at least 6 months with clinically determined treatments and for another 6 weeks given imipramine alone (up to 150 mg daily) prior to randomization. Prospective treatment arms included imipramine with lithium carbonate, imipramine plus placebo, and lithium plus placebo for a mean of 11 months. Treatment with lithium (with or without antidepressant continued) reduced depressive relapses 3- to 8-fold (20% with lithium vs. 76% with placebo). Among unipolar depressed patients considered separately, relapse rates were 20% with lithium versus 91% with placebo. In the bipolar II cases, depressive recurrence rates were similarly lower (20%) than with placebo (60%), although this difference was nonsignificant ($p = .12$). Imipramine was not significantly effective in any analysis, including unipolar depression. Although the findings appear to support the effectiveness of lithium against recurrent bipolar or unipolar depression, no apparent benefit of imipramine was found. However, the failure to detect a beneficial effect of imipramine in nonbipolar depressed patients and selection of stable patients limit interpretation of these findings.

Prien et al. (1984)

A fifth controlled trial[15] involved 117 patients diagnosed with RDC bipolar I disorder and randomly assigned to maintenance treatment for 2 years following initial stability for at least 2 months of treatment with lithium carbonate plus imipramine.[15] Treatment options were continuation of the combination or use of each agent alone. Risk of at least 1 recurrence with lithium alone was 29% for depressive and 26% for manic episodes; with lithium plus imipramine, corresponding rates were 22% and 28%, suggesting that addition of imipramine to lithium neither reduced depressive recurrence risk nor increased risk of mania. Moreover, imipramine and lithium given alone yielded nearly identical risks of a depressive recurrence (28% and 29%, respectively). However, imipramine monotherapy significantly increased risk of mania (53% vs. 28% with imipramine plus lithium and 26% with lithium alone; $\chi^2 = 10.2$, $df = 2$, $p = .038$). In this study protocol, sudden discontinuation of lithium may have contributed to elevation of the observed mania rate in the imipramine monotherapy group.[18] Notably, only 33% of subjects remained stable on treatment with lithium or lithium plus imipramine for 2 years. Kaplan-Meier survival analysis indicated that imipramine plus lithium did not lead to better outcome than lithium alone, although both lithium-treated groups outperformed imipramine alone.

Sachs et al. (1994)

In this first study of a nontricyclic antidepressant in bipolar depression,[16] 15 patients with DSM-III-R bipolar I disorder (given 19 treatment trials) received bupropion (9 trials) or desipramine (10 trials) in double-blind crossover additions to ongoing lithium maintenance treatment for up to 12 months. All patients were initially experiencing an acute major depressive episode. Efficacy rates were similar for both agents (50% for desipramine, 55% for bupropion). Adding desipramine led to acute mania in 5 (50.0%) of 10 trials, 2 within 8 weeks, whereas bupropion led to acute mania in 1 (11.1%) of 9 trials within 8 weeks ($\chi^2 = 3.0$, $df = 1$, $p = .07$). However, only 5 desipramine-treated, and 3 bupropion-treated patients continued for longer than 8 weeks. These small numbers, lack of placebo controls, and absence of information on total duration of follow-up make it difficult to draw definitive conclusions regarding long-term antidepressant effects of these agents or their relative safety in bipolar depression.

Amsterdam et al. (1998)

This study[17] involved retrospective analysis of 80 patients with DSM-III-R bipolar II disorder treated with fluoxetine versus placebo for up to 62 weeks, included with 661 unmatched and 89 matched patients with unipolar major depression, all of whom had been treated in the same multicenter clinical trial of depression. Risk of a depressive recurrence by 62 weeks was 50% with fluoxetine in bipolar II depressed patients and 69% in the unipolar depressed patients. Hypomania occurred in 5.0% (4/80) of the bipolar II subjects (3 within 8 weeks), compared with 0.30% (2/661) of unmatched unipolar cases and 0% (0/89) of matched unipolar cases ($\chi^2 = 22.7$, $df = 2$, $p \leq .001$). Hypomania was reported incidentally, and its assessment was not intrinsic to the study. Fluoxetine was replaced by placebo at various times, and the number of fluoxetine-treated subjects diminished over time (35% remained in the protocol for 6 months, and only 10% completed 62 weeks), but data pertaining to placebo treatment and relative effects of placebo versus antidepressant on depressive recurrence risks were not reported. Lack of certainty about diagnosis and outcome assessments, the diminishing number of fluoxetine-treated patients over time, and lack of direct comparisons of depressive and hypomanic risks with antidepressant versus placebo in bipolar II versus unipolar subjects all severely limit interpretation of the results reported. Nevertheless, the observation that acute hypomania with fluoxetine was more frequent in bipolar II subjects than in apparently unipolar depressed patients is plausible.

DISCUSSION

We found only 7 pertinent, controlled, blinded studies pertaining to long-term use of antidepressants for prevention of recurrent depression in bipolar disorder patients.[11–17] They involved a total of 256 bipolar I and 107 bipolar II (363 total) subjects; 3 trials included a placebo condition and 6 involved active-treatment comparisons (see Table 1). Given the variety of antidepressants and mood stabilizers available for several decades and the high prevalence and lethality of bipolar depression, the number of long-term, controlled trials is surprisingly small and the overall quality and quantity of evidence pertaining to risks and benefits of long-term use of antidepressants against recurrences of bipolar depression are surprisingly limited. The studies identified generally do not support the proposal that adding an antidepressant to ongoing lithium maintenance treatment substantially increases protection against bipolar depressive recurrences. Moreover, only imipramine, desipramine, bupropion, and fluoxetine among antidepressants, and only lithium among mood stabilizers, have been studied in this context. A 1-year outcome study by the Stanley Foundation Bipolar Network is now comparing effects of adding bupropion, venlafaxine, or sertraline to mood stabilizer therapy for bipolar depression. Preliminary impressions suggest that hypomanic episodes were not uncommon (approximately 12% per year) when the antidepressants were included.[19]

Although proof of superior protection from recurrences of bipolar depression by including an antidepressant in long-term regimens is lacking, the available evidence supports the widely accepted view that use of an antidepressant alone, and perhaps even adding one to ongoing mood-stabilizing treatment, can increase affective instability or cycling rates and the risk of switching into mania, hypomania, and perhaps mixed, agitated-dysphoric mood states.[3,6,8,9,12] Therefore, on balance, the available research suggests a possible unfavorable risk/benefit relationship for routine addition of long-term antidepressant treatment to ongoing mood stabilization with lithium, as well as a substantially increased risk of mood-destabilization when an antidepressant is used without lithium. However, given the rarity and limitations of studies that address these issues, these conclusions remain tentative, and additional studies are urgently required to compare effects of modern antidepressants added to proposed alternatives to lithium.

Despite limited evidence of long-term, added effectiveness and safety of antidepressants in bipolar disorders, they are used very commonly in contemporary clinical practice,[6,9,10] evidently reflecting the clinical reality that suffering from bipolar depression is compelling to both patients and clinicians, perhaps encouraging overuse of antidepressants. In addition, it is likely that benefits of long-term mood-stabilizing treatment for bipolar depression are not as widely appreciated as their benefits against recurrences of mania.[2,4,6,20,21] Indeed, product information bulletins pertaining to the use of lithium or anticonvulsants in bipolar disorder continue to comment only on recurrences of mania as an indication for long-term use and do not specifically mention prophylaxis for bipolar depression.[22] This narrow range of indications reflects the fact that no pharmaceutical company has presented data to the U.S. Food and Drug Administration (FDA) from tests showing long-term efficacy and safety of proposed mood-stabilizing agents for bipolar depression. Commercial interest in expanding FDA-approved indications for unpatentable lithium is very limited, but even modern drugs, including divalproex sodium and olanzapine, are, to date, FDA-approved only for acute mania. Until recently, evidence of their long-term protective effectiveness against both depressive and manic phases of bipolar disorders remained unavailable.[6,19] An exception is a recent double-blind divalproex maintenance study that reported a statistical trend for fewer depressive symptoms in 12-month outcomes with divalproex versus placebo.[23] Also of interest is whether lamotrigine, with demonstrated short-term antidepressant activity in bipolar disorder,[24] can sustain this benefit long-term.[25]

A common sense–based, balanced proposal would include recognition that antidepressants are probably less likely to induce short-term mood instability if used with a mood stabilizer,[15,26] although risk of long-term mood destabilization cannot be completely excluded.[1,13] It may be appropriate to reserve adjunctive addition of an antidepressant for cases of severe bipolar depression that fail to respond to adequate trials of 1 or 2 mood stabilizers, with exceptions for markedly suicidal depressive episodes in which case antidepressants might be warranted early in treatment.[27] Selection of a short-acting, nonlethal antidepressant in moderate doses for a limited time appears to be a prudent option for treating bipolar depressed patients. In addition, a trial period with no antidepressant should be considered at some point in treatment, and continuous long-term antidepressant use should be reserved for patients who repeatedly relapse into depression on discontinuation of antidepressants.

In conclusion, safe and effective treatments for acute and recurrent bipolar depression remain one of the most significant and least well investigated challenges pertaining to the major mood disorders. Intermittent and prolonged use of antidepressants in the treatment of bipolar I and II disorder patients, although not uncommon, is clearly not evidence based. Acquiring extensive data on the effectiveness and clinical safely of long-term treatment of bipolar depression with antidepressants, in comparison with mood-stabilizing medication alone, will require extensive and expensive trials involving complex pharmaceutical interests. Nevertheless, this clinically important and long-overlooked subject can and should be studied. Specifically needed are systematic studies of specific modern anti-

depressants combined with specific emerging alternatives to lithium as potential mood-stabilizing agents compared with the latter agents given alone. Such trials should give due consideration to risks involved in making rapid changes in ongoing mood-stabilizing treatment.[18,28] In particular, it seems essential to acknowledge that short-term efficacy in acute mania is not an adequate basis for evaluating the requirements of proposed mood-stabilizing treatments. Required is evidence of long-term effectiveness, not only against mania, but also against bipolar depression and its closely related risk of suicide.[7]

Drug names: bupropion (Wellbutrin), desipramine (Norpramin and others), divalproex sodium (Depakote), fluoxetine (Prozac), lamotrigine (Lamictal), olanzapine (Zyprexa), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

REFERENCES

1. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study [CME]. J Clin Psychiatry 2000;61:804–808
2. Tondo L, Baldessarini RJ, Hennen J, et al. Lithium maintenance treatment: depression and mania in bipolar I and II disorders. Am J Psychiatry 1998; 155:638–645
3. Goodwin FK, Jamison KR. Manic Depressive Illness. New York, NY: Oxford University Press; 1990
4. Kalin N. Management of the depressive component of bipolar disorder. Depress Anxiety 1997;4:190–198
5. Bowden C. Strategies to reduce misdiagnosis of bipolar depression. Psychiatr Serv 2001;52:51–55
6. Baldessarini RJ, Tarazi F. Drugs and the treatment of psychiatric disorders. In: Hardman J, Limbird L, Molinoff P, et al, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill Press; 2001. In press
7. Tondo L, Baldessarini RJ. Reduced suicide risk during lithium maintenance treatment. J Clin Psychiatry 2000;61(suppl 9):97–104
8. Zornberg GL, Harrison GP. Treatment of depression in bipolar disorder: new directions for research. J Clin Psychopharmacol 1993;13:397–408
9. Ghaemi SN, Sachs GS, Chiou AM, et al. Is bipolar disorder still underdiagnosed? are antidepressants overutilized? J Affect Disord 1999;52: 135–144
10. Health I. National Disease and Therapeutic Index. Plymouth Meeting, Pa: IMS America; 1998
11. Prien RF, Klett CJ, Caffey EM. Lithium carbonate and imipramine in prevention of affective episodes. Arch Gen Psychiatry 1973;29:420–425
12. Wehr TA, Goodwin FK. Rapid cycling in manic-depressives induced by tricyclic antidepressants. Arch Gen Psychiatry 1979;36:555–559
13. Quitkin FM, Kane J, Rifkin A, et al. Prophylactic lithium carbonate with and without imipramine for bipolar I patients. Arch Gen Psychiatry 1981; 38:902–907
14. Kane JM, Quitkin FM, Rifkin A, et al. Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness: a prospective, placebo-controlled comparison. Arch Gen Psychiatry 1982;39:1065–1069
15. Prien RF, Kupfer DJ, Mansky PA, et al. Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders: a report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. Arch Gen Psychiatry 1984;41:1096–1104
16. Sachs GS, Lafer B, Stoll AL, et al. A double-blind trial of bupropion versus desipramine for bipolar depression. J Clin Psychiatry 1994;55:391–393
17. Amsterdam J, Garcia-Espana F, Fawcett J, et al. Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. J Clin Psychopharmacol 1998;18:435–440
18. Baldessarini RJ, Tondo L, Viguera AC. Discontinuing lithium maintenance treatment in bipolar disorders: risks and implications. Bipolar Disord 1999;1:17–24
19. Post R, Leverich G. A Five Year Prospectus of the Stanley Foundation Bipolar Treatment Network, vol 8. Bethesda, Md: Stanley Foundation; 2000
20. Baldessarini RJ, Tondo L, Suppes T, et al. Pharmacological treatment of bipolar disorder throughout the life-cycle. In: Shulman K, Tohen M, Kutcher S, eds. Bipolar Disorder Through the Life-Cycle. New York, NY: John Wiley & Sons; 1996:299–338
21. Baldessarini RJ, Tohen M, Tondo L. Maintenance treatment in bipolar disorder. Arch Gen Psychiatry 2000;57:490–492
22. Physicians' Desk Reference. 55th ed. Montvale, NJ: Medical Economics; 2001
23. Bowden C, Calabrese J, McElroy S, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Arch Gen Psychiatry 2000;57:481–489
24. Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind, placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. J Clin Psychiatry 1999;60:79–88
25. Calabrese JR, Suppes T, Bowden CL, et al. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. J Clin Psychiatry 2000;61:841–850
26. Bottlender R, Rudolf D, Straub A, et al. Mood-stabilisers reduce the risk of developing antidepressant-induced maniform states in acute treatment of bipolar I depressed patients. J Affect Disord 2001;63:79–83
27. Sachs G, Printz D, Kahn D, et al. The Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder. Postgrad Med 2000;(4, spec no.):1–104
28. Baldessarini RJ, Tondo L. Recurrence risk in bipolar manic-depressive disorders after discontinuing lithium maintenance treatment: an overview. Clin Drug Invest 1998;15:337–351